Specialty Conference

Medical Risks of Cocaine Use

Discussant
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Cocaine abuse can lead to a life-threatening illness. When patients present for treatment of its complications, they rarely volunteer information concerning their personal use of cocaine. Excited delirium is often the first stage of one of the life-threatening complications that may include myocardial infarction, subarachnoid hemorrhage, and intestinal ischemia or infarction. Two other presentations in which cocaine abuse should be considered are spontaneous abortion and pneumomediastinum. While the incidence of such adverse outcomes is unknown, these complications represent unique risks for the growing number of cocaine abusers.

CAROL KURTZ BATES, MD*: Reports of illness associated with cocaine use have been prominent in both the medical and lay literature. In June 1986 national media attention focused on the issue of sudden death in cocaine users when two prominent, healthy athletes died of presumed cocaine toxicity. A variety of nonfatal pathophysiologic events have also been attributed to cocaine use. In particular, a number of reports of premature cardiac events have appeared in medical journals in recent years. In this discussion, I will review the data linking cocaine use with a number of reported consequences, including sudden death, cardiac toxicity, pulmonary effects, and adverse outcomes in pregnancy.

Sudden Death and Cocaine Use

Sudden death has been reported in several different settings of cocaine abuse. Len Bias, a basketball player and one of the above-mentioned athletes, was said to be a first-time user. Chronic abusers have also died from cocaine reactions, sometimes without a known change in their dose of use. The syndrome has also been clearly described in "body packers" who ingest large quantities of wrapped cocaine for the purpose of smuggling.[1]

The magnitude of the problem has not been well defined. Data from two representative series follow. During a two-year period in Los Angeles County, 20 deaths were ascribed to cocaine; in 18 of those, cocaine was the only illicit substance identified.[1] A larger series was reported from Dade County in Florida, where 60 deaths were attributed to cocaine over four years.[2] Of these deaths, 92% were thought to be accidental.

Data with respect to what represents a lethal dose of cocaine in humans remain murky at best. First, historical data quantitating doses of drugs in recreational settings are often unavailable or unreliable. Much of the data is, therefore, pieced together from postmortem blood levels, which have varied widely.[1-3] This information is further confounded in that cocaine probably continues to be metabolized after death. Metabolites of cocaine have rarely been measured.[2,3] Animal studies have not been very helpful in defining the lethal dose of cocaine because of substantial variation among species. A rough summary of available animal data would point to a lethal dose of about 100 mg per kg. For comparison, the often-quoted "safe" dose for local anesthesia is 200 mg. Fatalities, however, have been reported with doses of cocaine as low as 25 mg. The average fatal dose in humans is said to be 1.4 gm.[4]

When death occurs, it may be the end result of a rapid progression through a phenomenon that has been termed the "cocaine reaction." This has been described mainly by physicians at the Haight-Ashbury Clinic in San Francisco and has also been called the "Casey Jones" reaction.[5] Patients with cocaine toxicity are said to progress through several stages.

Most patients will have mild toxicity and will not progress beyond stage one. Findings include many behavioral changes: restlessness, pressured speech, and teeth grinding. Examination reveals tachycardia, hypertension, tachypnea, and hyperthermia. Pupils are dilated but reactive. Patients are often tremulous, diaphoretic, and pale.

When patients progress to the stage of advanced stimulation, they are usually unresponsive to stimuli, hyperreflexic, and may have seizures and ventricular arrhythmias. If untreated, they may die. A similar sequence of events has been observed in the dog model for cocaine overdose. Progression through these stages may occur within a few minutes to a few hours.

An interesting variant of the cocaine reaction was described by a group in Miami.[6] They observed seven fatalities preceded by an "excited delirium." Police were called to restrain patients who were often shouting, thrashing, and otherwise physically violent. These patients progressed to cardiopulmonary arrest on the scene or during transport in police custody.

Observations made in body packers have also helped to define the syndrome of acute cocaine toxicity. As mentioned previously, body packers, or "mules," ingest many packets of

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wrapped cocaine for transport. Packets are swallowed or are inserted in the rectum or vagina.

These persons have almost always returned very recently from South America. It is thought that this is currently a common method of importing cocaine and that most smugglers survive the experience. Toxicity only occurs when the packages rupture or leak through a semipermeable membrane. When toxicity occurs, symptoms match those noted earlier, including hypertension, tachycardia, hyperthermia, mydriasis responsive to light, and seizures.[7,8]

Suspicion of body packing can be confirmed with an abdominal x-ray film. Multiple well-defined densities in the stomach, small bowel, and colon are seen.[9,10] Densities in the stomach and ascending colon are more easily distinguished from stool. Occasionally, one may see an oblong density with a rosette at one end. The so-called double condom sign is one in which a crescent of air surrounding an ovoid density is seen. It is thought that air trapped in the layers of wrapping produces this phenomenon.

Body packers who do not show signs of cocaine toxicity can be managed conservatively. A series of 50 patients from a jail ward in Florida were followed medically.[10] There were 54 to 182 packets seen per patient. On the average, these patients took 28 hours to pass all of their packets. Once they began to pass packets per rectum, they were treated with mineral oil. Evacuated packets were carefully examined for evidence of wrapper deterioration. When abdominal x-ray films confirmed elimination of all packets, the patients were discharged. Operations were performed for signs of obstruction, cocaine toxicity, or any evidence of packet decay. In this series, a total of 9 patients required operation, and there were no deaths.

For patients who show signs of cocaine toxicity from body packing or other routes of ingestion, management is as outlined in Table 1. Obviously, if the patient has respiratory or cardiac arrest, airway protection and cardiopulmonary resuscitation are indicated. Because of the frequency of hyperthermia in these patients, it is important to follow the core temperature.

Diazepam is the recommended therapy for agitation and other behavioral manifestations of toxicity.[5,11] Interestingly, hypertension, tachycardia, and other signs of catechol excess have been reported to respond to diazepam. Although it has not been used extensively in humans, chlorpromazine pretreatment in the dog model prevents the cardiovascular manifestations of toxicity as well as hyperthermia, acidosis, and death.[12] Propranolol has been used clinically, but in the experimental setting it does not prevent death.[12,13] There is one report in the literature of propranolol-induced hypertension during treatment of cocaine intoxication.[14] It is speculated that propranolol may block both β_1 and β_2 receptors, leaving unopposed α-adrenergic receptor stimulation. It may, therefore, be preferable to use a β_1 selective agent or a combined alpha-beta blocker, although there is little reported experience with this. Finally, calcium channel blockers may also have a role in treating cocaine toxicity. In a study using dogs, pretreatment with nitrendipine substantially increased survival time and the size required for a dose to be lethal.[15]

In summary, patients who present with agitated delirium or signs of catechol excess should be monitored, given the risk of their progressing to arrhythmias and seizures. Treatment modalities most commonly used include diazepam and beta blockade, although chlorpromazine and calcium channel blockers may also be effective. The risk of sudden death in cocaine use, however, is not well defined.

TABLE 1.—*Management of Cocaine Reaction*

1. ABCs—airway, cardiopulmonary resuscitation
2. Follow core temperature
3. Diazepam 2.5 to 5 mg IV q 5 min as needed
4. ? beta-blocker for hypertension or ectopy
5. ? calcium-channel blockers
6. ? chlorpromazine

Cardiac Toxicity

A 1986 report of seven patients with presumed cardiac toxicity[16] was only one of many detailing cocaine use and cardiac toxicity. Reported cardiac events attributed to cocaine use include myocardial infarction,[16-28] arrhythmias,[16,29-31] aortic rupture,[32] and myocarditis.[16,24] Myocardial infarction has been the most frequently reported event. Table 2 provides data on the 23 reported cases of myocardial infarction associated with cocaine use. A number of points can be made. First, the age range of reported cases is 19 to 44 years. The mode of ingestion of the drug was quite variable, but more than a half used cocaine intranasally. Many of these patients had confounding risk factors for coronary disease; over 50% were smokers. A number of the patients abused other substances, including heroin and marijuana. Finally, most had obstructive coronary artery disease when studied with angiograms. Of note, however, is that eight patients had normal coronary arteries; four of these eight were studied with ergonovine challenge, which produced negative results in all patients.

There are a number of obvious problems with these data. First, this is retrospective information. No one has studied these patients with cocaine challenge in the cardiac catheterization laboratory. Second, the coronary anatomy of this group of patients was heterogeneous. In a few patients, anatomy was unknown. Of more concern is that the temporal relationship between cocaine use and infarction varied widely. Some patients were said to develop pain immediately, but in one patient, pain occurred more than 24 hours after use but was still attributed to cocaine. Finally, it is possible that other abused substances played a role in the results with some of these patients.

A number of mechanisms may account for cocaine-induced ischemia.[33,34] Cocaine clearly can increase myocardial oxygen demand given the common findings of hypertension and tachycardia. Oxygen demand may also increase because of increased contractility. Moreover, cocaine is commonly cut with a number of substances, including amphetamines, which are well documented as increasing myocardial oxygen demand. It has been postulated that cocaine increases the tendency for thrombosis, but there is no experimental support for this idea. Another potential mechanism is that of vasospasm either via a direct effect of cocaine or via sympathetic potentiation. If this is indeed the mechanism, ergonovine is unlikely to help in the clinical setting given the history of negative studies in this population. Finally, both coronary emboli and coronary vasculitis could be potential mechanisms, but there has been no evidence for these phenomena clinically or pathologically.

It is not possible to unequivocally state that cocaine abuse causes myocardial infarction. The association appears to be a strong one, however, and a number of observations can be

made. First, the association appears to be independent of the route of ingestion. Second, the time of onset of ischemia following cocaine use is unknown. Third, cardiac toxicity is not clearly dose-related. In patients with obstructive coronary artery disease, cocaine probably can induce ischemia or infarction because of the increase in myocardial oxygen demand. In a young patient with ischemia or infarction, one should have a heightened suspicion of cocaine use given the number of case reports. Finally, as is true of the data on sudden death in cocaine users, the incidence of myocardial infarction or ischemia is totally unknown.

There are other types of cardiac toxicity that have been attributed to cocaine use. Supraventricular arrhythmias have been seen.[31] Several patients have been reported to have ventricular tachycardia or fibrillation unassociated with myocardial infarction but temporally related to cocaine use.[16,29,30] Only one reported patient was studied extensively.[16] He had ventricular tachycardia followed by fibrillation after snorting approximately 500 mg of cocaine. Cardiac catheterization, ergonovine stimulation, and electrophysiologic studies were all normal in this patient, suggesting that he had no underlying cardiac disease.

Reviews of the medical consequences of cocaine use commonly mention aortic rupture as a complication. In fact, there is only one report of this in the literature: A 45-year-old free-base user had a ruptured aorta at autopsy, probably because of hypertension associated with cocaine ingestion.[32]

Cardiomyopathy has also been reported in this setting. Several patients, not surprisingly, have had a fall in ejection fraction following myocardial infarction.[26,27] There are also reports of a syndrome in cocaine users similar to postviral myocarditis. One patient had biopsy-proved myocarditis that responded to therapy with prednisone and azathioprine.[16] Another report is based on autopsy findings in a 21-year-old with sudden death following cocaine use. He had a documented anterior myocardial infarction but also had lymphocytic myocarditis.[24] Reportedly, the autopsy on Len Bias showed tiny foci of lymphocytes and macrophages infiltrating myocardium.[35] These case reports have led some investigators to suggest the concept of a cocaine-induced toxic cardiomyopathy.[27] Although this may be true, these patients instead may have had viral or idiopathic myocarditis incidental to cocaine use.

There are a number of other vascular events that have been attributed to cocaine. There have been two case reports of intestinal ischemia associated with cocaine use.[36] Literature on cerebrovascular events is more extensive. There are four reported cases of subarachnoid hemorrhage in cocaine users.[37-39] One of these patients had an aneurysm of the anterior communicating artery and another had a posterior communicating aneurysm. A third had an arteriovenous malformation. There are two reported cases of parenchymal central nervous system hemorrhage[38,40] and two cases of bland infarction.[38,41] Once again, the mechanism of hemorrhage is thought to be a sudden rise in blood pressure causing the rupture of a preexisting lesion. Those who have seen these patients warn that headache associated with cocaine use may be a symptom of an unsuspected aneurysm or arteriovenous malformation.[33]

Pulmonary Effects

As mentioned previously, vascular toxicity is independent of the route of ingestion of cocaine. In contrast, most forms of pulmonary toxicity are associated with a single route of ingestion. In particular, free-basing appears to have a number of adverse effects on the lungs.

TABLE 2.—*Myocardial Infarctions Attributed to Cocaine*

Reference	*Age/Sex*	*Route*	*Dose*	*Temporal Relation*	*Infarct Location*	*Coronary Anatomy*	*Smoking*	*Other Drugs*
Coleman et al[17]	38/♂*	Intranasal	0.5 g	?	Anterolateral	?	Yes	...
Kossowsky and Lyon[18]	27/♂*	Intravenous	?	?	Anterior	?	...	Heroin
	30/♂	Intravenous	?	?	Anterolateral	100% LAD	Yes	Heroin/alcohol
	35/♂	?	?	?	Anterior	90% LAD	...	...
	36/♂	Intravenous	?	?	Anterior	75% LC	...	Heroin
	43/♂	Intranasal	?	'Soon after'	Inferior	100% RCA	...	...
	44/♂	Intranasal	'6 lines'	'Shortly after'	Inferoposterior	?	Yes	...
Schachne et al[19]	21/♂	'Inhaled'	0.25 g	5 h	Inferior	Normal	...	...
Pasternack et al[20]	35/♂	Intranasal	?	?	Anterior	LAD, LC, RCA stenoses	Yes	...
	37/♂	Intranasal	?	?	Anterior	LAD stenosis	Yes	...
	38/♂	?	?	?	Anterior	LAD stenosis	Yes	...
Howard et al[21]	28/♀	Intranasal	1.5 g	5 h	Anterior	Normal †	...	...
Cregler and Mark[22]	38/♂*	Intranasal	?	45 min	Inferior	Normal †	Yes	Heroin/alcohol
Gould et al[23]	32/♂	Cocaine/tobacco cigarette	?	1 h	Anterolateral	...	Yes	...
Simpson and Edwards[24]	21/♂	Intravenous	?	30 min	Anterior	LM, LAD thrombus	Yes	Marijuana/ alcohol
Weiss[25]	19/♂*	Intranasal	?	'Just prior'	Inferior	60% RCA, 40% LAD	Yes	...
Rollingher et al[26]	42/♂	Intravenous	?	2 h	Anterior	Normal	Yes	Alcohol
Weiner et al[27]	42/♂*	Intranasal/IV	?	> 24 h	Anterior	Normal	Yes	Heroin/alcohol
Wilkins et al[28]	33/♂	Intranasal	2.0 g	'After an evening'	Anterior	Normal	...	...
Isner et al[16]	29/♂	Intranasal	1.0 g	1 h	Inferior	?	Yes	...
	28/♀	Intranasal	?	6 h	Anterolateral	Normal †	...	...
	37/♂	Intranasal	?	?	Anterior	100% LAD	...	...
	23/♂	Intranasal	?	11 h	Inferior	Normal †	...	...

LAD=left anterior descending, LC=left chamber, RCA=right coronary artery, LM=left main

*These patients had recurrent infarctions.
†Ergonovine stimulation during cardiac catheterization induced no spasm.

A group in Chicago did pulmonary function testing in 19 free-base users.[42] The only significant abnormality found was that of a decrease in diffusing capacity. Total lung capacity and one-second forced expiratory volume were greater than 80% predicted. Ten of 19 patients had a diffusing capacity of less than 70% of predicted. Symptoms of cough and dyspnea were reported in 63% of patients but were more common in those with impaired diffusing capacity. Interestingly, duration of use was not predictive of impairment. Tobacco use and age also did not correlate with impairment.

Free-basing has also been associated with pneumomediastinum.[43-48] There are at least seven reports of patients who developed this after a Valsalva's maneuver or partner-applied positive pressure. Patients may also have pneumopericardium and pneumothorax. Symptoms include pleuritic pain and dyspnea. Examination may elicit Hamman's sign or a mediastinal crunch. The mechanism is thought to be an alveolar rupture with dissection of air to the mediastinum. Treatment is conservative; few patients have required chest tube drainage. The major differential diagnosis in this setting is that of esophageal rupture, which can be ruled out with an esophagogram.

Additional pulmonary complications of cocaine use are impaired diffusing capacity of the lung for carbon monoxide (DLCO), pneumomediastinum, bronchiolitis obliterans, pulmonary edema, and nasal septal perforation and sinusitis. Bronchiolitis obliterans has been reported in two free-basers.[49] Noncardiogenic pulmonary edema has occurred in cocaine users and is not specific for any route of ingestion.[1,2,6,7,50] A number of upper airway problems have been noted with the intranasal use of cocaine. The incidence of nasal septal perforation may have been exaggerated, but it certainly does occur.[1] Cocaine probably causes mucoperichondrial ischemia followed by necrosis.[40,51] Earliest symptoms of a septal defect include whistling on inhalation, nasal crusting, and bleeding. The differential diagnosis of septal defects includes collagen vascular disease, tuberculosis, leprosy, tertiary syphilis, and trauma. Other upper airway problems include sinusitis and osteitis.

Cocaine and Pregnancy

Cocaine use has also been associated with adverse outcomes in pregnancy. In 1985 pregnant women who were cocaine or heroin users or both were studied.[52] The study was not controlled for tobacco, alcohol, or marijuana use. Heroin users were given methadone. Almost all cocaine use was intranasal. The major finding was a higher rate of spontaneous abortion in cocaine users than in those who used heroin or in a control group. Four patients had abruptio placentae, with all episodes of abruption occurring after intravenous cocaine use. Infants born to cocaine users were jittery and had depression of interactive behavior. There was little evidence of teratogenicity in this study. Only one cocaine user had an infant with prune-belly syndrome. Infant growth was not affected.

Abruptio placentae was thought to occur because of maternal hypertension. Spontaneous abortion was thought to be due to placental vasoconstriction and increased uterine contractility. A study on pregnant ewes supports this hypothesis.[53] This study looked at both maternal and fetal hemodynamics. Shortly after cocaine injection, maternal blood pressure increased, uterine vascular resistance increased, and uterine blood flow fell. Fetal oxygenation then fell, while the fetal heart rate increased. Interestingly, when cocaine was injected directly into the fetus, the heart rate and blood pressure increased but oxygenation remained stable. Thus, placental vasoconstriction was confirmed in this model. The observed fetal hypoxia appeared to be due to decreased placental blood flow and was not a direct effect of circulating cocaine in the bloodstream of the fetus.

In summary, both human and animal studies suggest that cocaine use in pregnancy is associated with an increased incidence of abruption and spontaneous abortion. Infant behavior is also abnormal.

TABLE 3.—*Toxicity by Route of Ingestion*

Route	Result
Any	Sudden death, cardiac toxicity, subarachnoid hemorrhage, other vascular events, pulmonary edema
Intravenous	Endocarditis, hepatitis, human immunodeficiency virus infection, abscesses
Free base	Cough, sore throat, impaired diffusing capacity, pneumomediastinum
Intranasal	Nasal septal perforation, anosmia, sinusitis, osteitis

Routes of Cocaine Ingestion

Having reviewed cocaine toxicity through a tour of the organ systems, I am going to briefly review toxicity according to routes of ingestion (Table 3). As noted before, sudden death, cardiac toxicity in general, subarachnoid hemorrhage, and other vascular events can occur with any form of cocaine use. The problems peculiar to intravenous abuse have not been stressed because they may occur with intravenous use of any illicit drug. These complications of intravenous drug abuse include endocarditis, hepatitis, human immunodeficiency virus infection, and abscesses. In particular, patients may get pulmonary or intracranial abscesses.[54] Free-base users may complain of cough or sore throat. They may have impaired diffusing capacity or may get pneumomediastinum. Snorting is associated with upper airway lesions such as nasal septal defects, sinusitis, and inability to smell or taste.

When patients present to primary care providers and subspecialists for treatment of complications of cocaine abuse, they may not volunteer information about their habit. A history of cocaine use should be pursued when patients present with an excited delirium, since this can be the first sign of a life-threatening illness. Vascular events such as myocardial infarction, subarachnoid hemorrhage, and intestinal ischemia in young patients are suspect. Pneumomediastinum and spontaneous abortion may also be clues to cocaine use. Nasal septal defects or other upper airway lesions may be presenting complaints. One might look for the "coker's dyad" of a gold coke spoon necklace and a bottle of nasal spray in the pocket.[5]

Educating an asymptomatic patient regarding the risks of cocaine use is a bit more troublesome. Most of the information on adverse effects of cocaine use is in the form of case reports. Although the array of these worrisome reports is impressive, the incidence of such adverse outcomes remains unknown. Assessment of risk to the individual cocaine user is thus impossible to make.

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